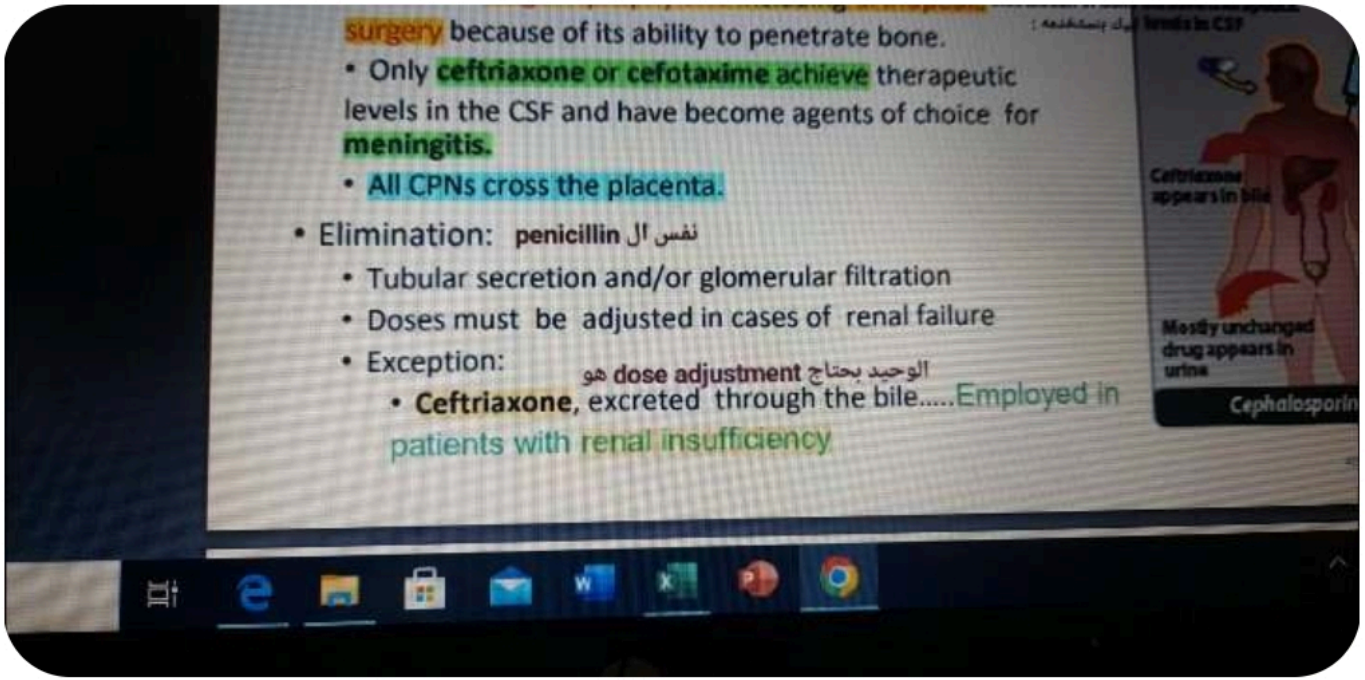
Artery Academy

Done By Mariam Yacoub

قبل ما نبلش تفريغ ، بدي انوّه على تعديل بسيط بالشابتر التاني ، وشكرًا للّي نبّهني عليه



ال **Ceftriaxone** هي إلّي ماااااااا بتحتاج **dose adjustment** وليس العكس لإنه أصلاً بصيرلها **excretion** عن طريق ال **bile** ف ما حتتأثر بال **renal insufficiency**

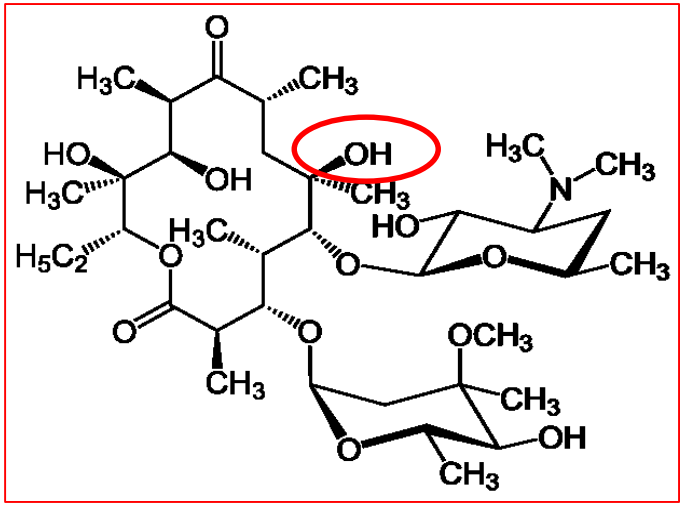
MACROLIDES and Ketolides

يلا نبلش ✔

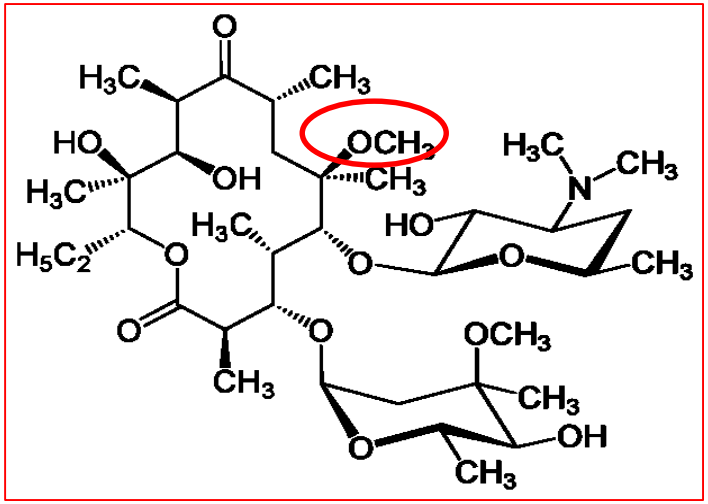
Macrolides

- The macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached.
- The prototype drug, **erythromycin**, was obtained in 1952 from *Streptomyces erythreus*.
- **Clarithromycin** and **azithromycin** are semisynthetic derivatives of erythromycin.

سبب التسمية : وجود حلقة كبيرة **macro** فيها ١٤-١٦ **atom**
الأساس وال **prototype** هو ال **erythromycin** لكن زي ما حكينا في
semisynthetic من ال **minocyclin** وهو ال **tigecyclin** ف هون برضو عندي
semisynthetic من ال **erythromycin** وهو ال **Clindamycin &**
azithromycin

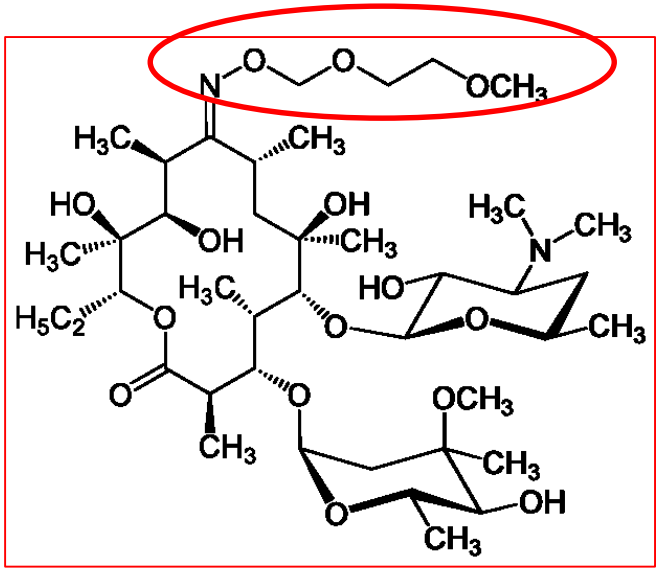


Erythromycin

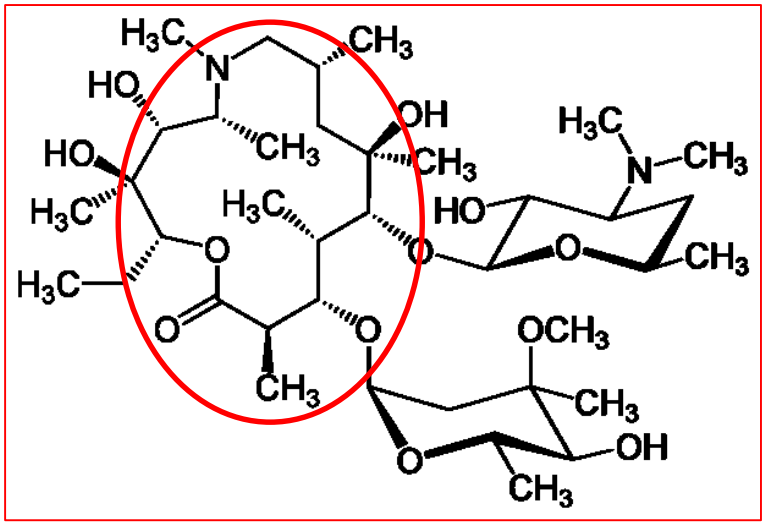


Clarithromycin

للإطّلاع فقط



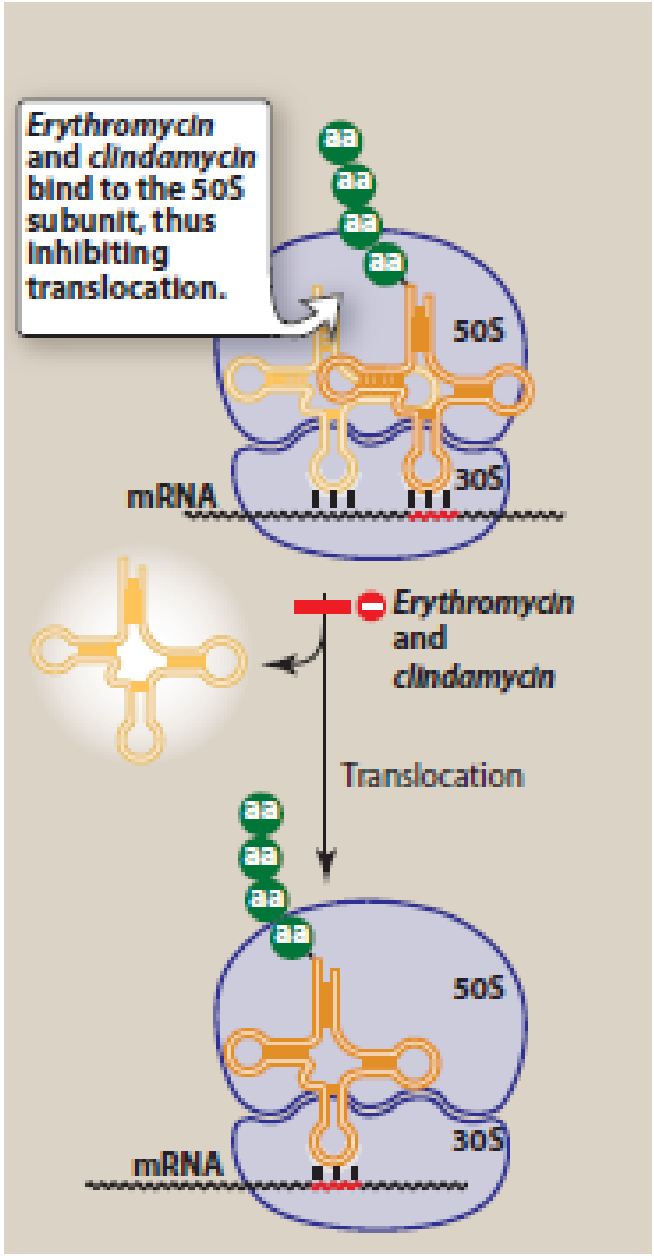
Roxithromycin



Azithromycin

Macrolides mechanism of action

- The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis.
- Generally considered to be bacteriostatic, they may be bactericidal at higher doses.



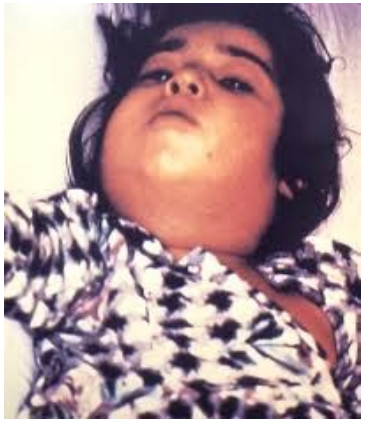
بدنا نركز على اختلاف المصطلحات ، ف مثلاً بال **tetracycline** كنا نحكي ارتباطه **reversible** وكان يعمل **inhibition** ل **initiation step** بينما ال **macrolide** ارتباطها بال **50s** وليس **30s** + ارتباطها **irreversible** + بتعمل **inhibition** لل **translocation step**

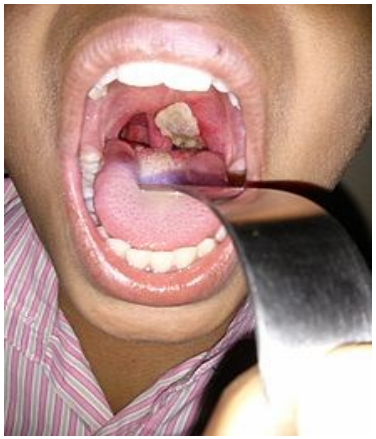
استخداماته بتتشابه مع ال **tetracycline**

Erythromycin indications

بديل للأشخاص إلّي عندها حساسية من ال **penicillin**

- **Same spectrum of** penicillin G (used in patients allergic to the penicillins with infections caused by staphylococci and streptococci)
- **Syphilis (**Treponema pallidum): alternative in case of allergy to penicillin G
- **Diphtheria (CORYNEBACTERIUM DIPHTHERIAE, G+, Upper RTI)**





اهم أعراضها انتفاخ زي ما هو
موضح بالمنطقة بالصورة عاليسار
+ سقف الحلق بكون **gray** وطبيعي
ما نشوف هاي الحالات عنا لإنه
بناخد مطعوم إلها

- **CHLAMYDIAL INFECTIONS**
  - **Alternative to Tetracycline (first choice for pregnant women)**

لإنه ممنوع عنهم **tetracycline**

- **MYCOPLASMAL PNEUMONIA**

اخر ٢ بنفضل بعلاجهم ال **azithromycin and doxycycline**

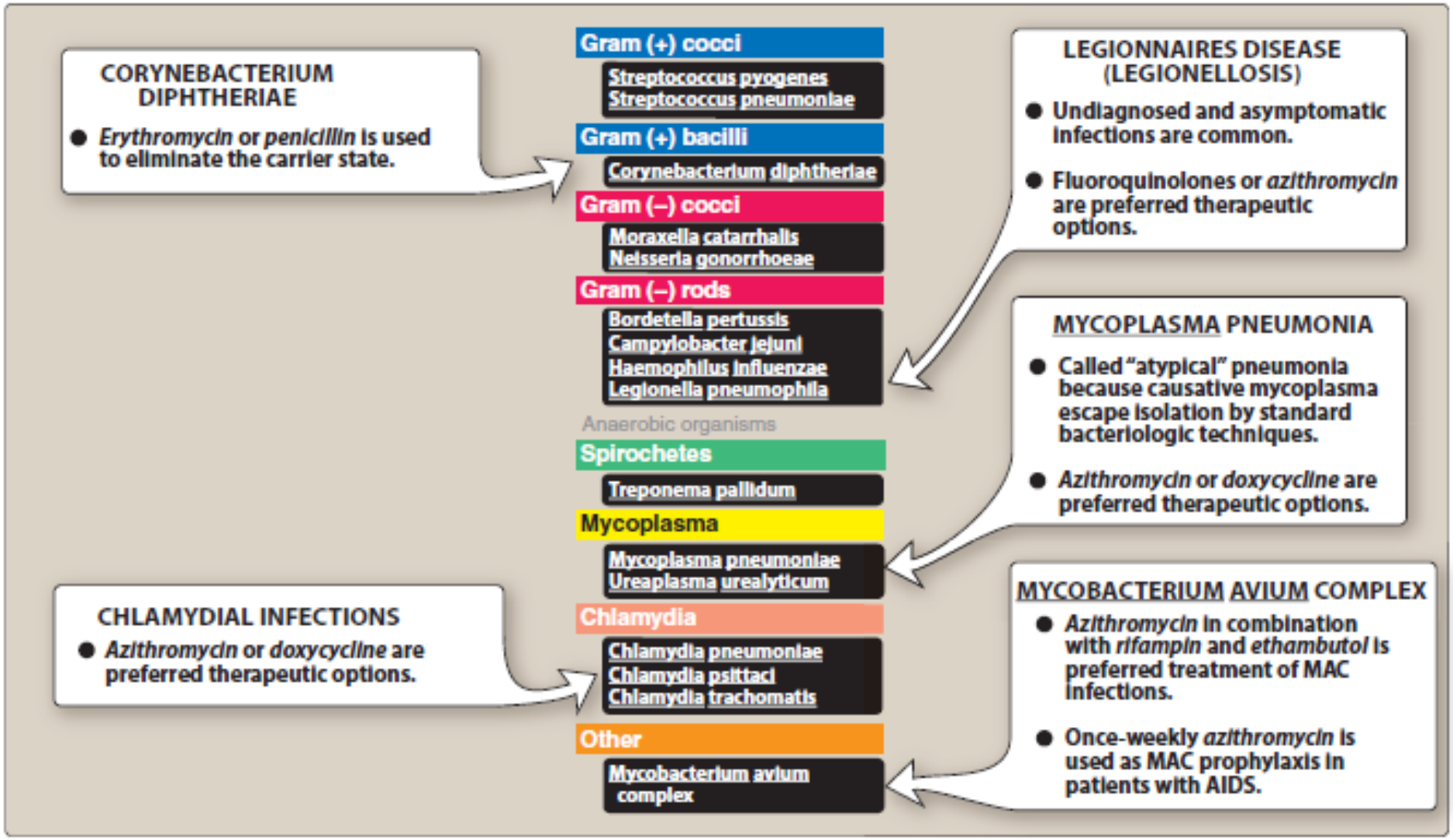


Figure 39.10
Typical therapeutic applications of macrolides.

بتفوق ال **clarithromycin** عن ال **erythromycin** بأربع نقاط رح احط عليهم هايلايتر

Clarithromycin

- Clarithromycin and erythromycin are similar with respect to antibacterial activity except that clarithromycin is more active against Mycobacterium avium complex. رح نحكي عنها بشكل موسّع بشابتر لحال
- Active against Haemophilus influenzae (RTI)
- The advantages of clarithromycin compared with erythromycin are lower incidence of gastrointestinal intolerance and less frequent dosing. أقل أعراض على ال **GI** لإنه بنعطي منه عدد جرعات أقل من ال **erythromycin**
  - The recommended dosage of clarithromycin is 250–500 mg twice daily or 1000 mg of the extended-release formulation once daily while erythromycin is given every 6 hours.

هون بحكيلك إنه ال **clarithromycin** بنعطيه **once , twice daily** بس !
بينما ال **erythromycin** بنعطيه كل ٦ ساعات ! ف هاي سلبية إله

كله بشبه ال **clarithromycin** لكن الفرق بأخر نقطة

Azithromycin:

- Its spectrum of activity, mechanism of action, and clinical uses are similar to those of clarithromycin.
  - Azithromycin is active against M avium complex.
  - Azithromycin is slightly less active than erythromycin and clarithromycin against staphylococci and streptococci and slightly more active against H influenzae.
  - Azithromycin is highly active against Chlamydia sp (Used for urethritis caused by Chlamydia trachomatis)
- Azithromycin does not inactivate cytochrome P450 enzymes and, therefore, is free of the drug interactions that occur with erythromycin and clarithromycin.

azithromycin ال ما بيعمل **inhibition of cytochrome P450** على عكس ال **erythromycin**
and clarithromycin ف لإنهم بيعملوله **inhibition** ف رح يكون الهم كتير **drug-drug interaction**

Resistance to macrolides

- Occurs in most strains of staphylococci
- Several mechanisms have been identified:

(1) reduced permeability of the cell membrane

(2) active efflux

(3) production (by Enterobacteriaceae) of esterases that hydrolyze macrolides

(4) modification of the ribosomal binding site (so-called ribosomal protection)

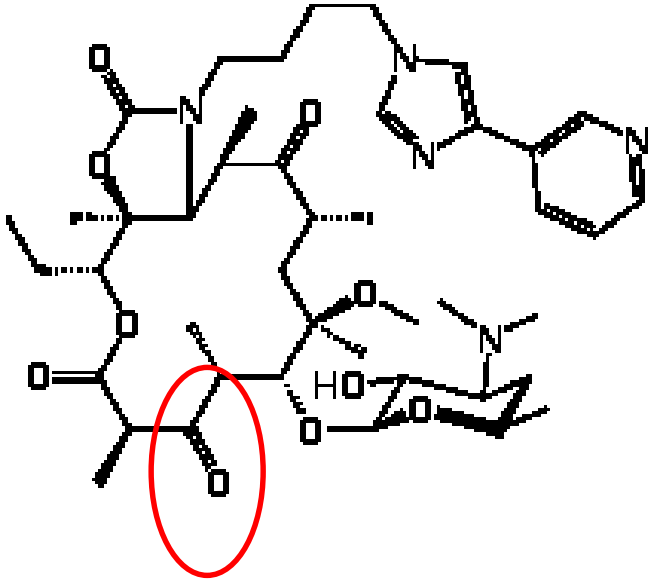
- Both clarithromycin and azithromycin show cross-resistance with erythromycin BUT **telithromycin** can be effective against macrolide-resistant organisms

نفس إلّي حكيناه سابقًا الخلية البكتيرية بتدافع عن نفسها بعدة طرق :
الأولى : إنها بتقلل ال **permeability of the cell membrane** ف بالتالي بتصعّب دخول ال **macrolides** لجوا الخلية ، وفي حال دخل ف بنعمل ال طريقة الثانية :
وهي **acrive Efflux** ف بتطلعُه لبرا ال **cytosol**
تالت طريقة بتنتج إنزيم ال **esterases** إلّي بكسّر ال **macrolides**
وختامها بال **ribosomes protection** وهي إنه بتغير موقع ارتباط ال **macrolides** بال **ribosome**

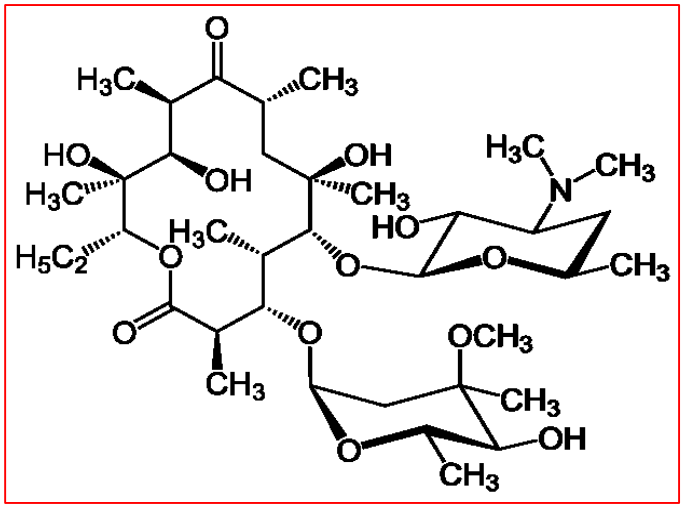
لكن صنّعوا نوع من ال **macrolides** بقاوم هاي ال **mechanism of resistance** وهو " **telithromycin**"

الهم نفس ال **macrocycle** لكن الاختلاف إنهم مربوطين ب **ketone** وليس **sugar**

KETOLIDES



- Ketolides are semisynthetic 14-membered-ring macrolides, differing from erythromycin by substitution of a 3-keto group for the neutral sugar L-cladinose.
- **Telithromycin** is approved for limited clinical use.
- Many macrolide-resistant strains are susceptible to ketolides because the structural modification of these compounds renders them poor substrates for efflux pump-mediated resistance, and they bind to ribosomes of some bacterial species with higher affinity than macrolides.



Erythromycin

استخدام ال **telithromycin** فقط بحالة وجود **resistance** من ال **macrolides** وبتميز ال **ketolides** إنه عنده **affinity** أعلى من ال **macrolides** بسبب عدم وجود ال **substrate** إلّي بخلي المركب يطلع لبرا الخلية وما يعمل شغله

Adverse effects

1. **Gastric distress and motility:** most common, may lead to poor patient compliance (especially with *erythromycin*). *Clarithromycin* and *azithromycin* seem to be better tolerated. Higher doses of erythromycin lead to smooth muscle contractions.
2. **Cholestatic jaundice:** This side effect occurs especially with the estolate form (not used in the United States) of erythromycin; however, it has been reported with other formulations.
3. **Ototoxicity**: Transient deafness has been associated with erythromycin, especially at high dosages. Azithromycin has also been associated with irreversible sensorineural hearing loss.

من الأعراض الجانبية إنه بيعمل :
١) بزيد ال **gastric distress and motility** بالذات الجرعات العالية من ال **erythromycin** بحيث إنه بيعمل **stomach muscles contraction** وبزيد ال **spasm** في المعدة لهيك صاروا يستخدموا لمرض اسمه **Gastroparesis** لحتى تزيد ال **motility** عند هاد الشخص
٢) وجدوه فقط في ال **estolate form of erythromycin** وهو ال **cholestatic jaundice** وسجلوه بتركيبات تانية لكن هاد اكتر شي
٣) بيعمل **ototoxicity** وخاصة ال **erythromycin** بالجرعات العالية وال **azithromycin** ممكن يعمل فقدان للسمع بشكل **irreversible**

ملاحظة : ال **azithromycin** ما بعمل **inhibition of cytochrome P450** لا تنسوا !

Drug interactions

حكيناها سابقًا إنهم بيعملوا **inhibition of cytochrome P450** ف
بالتالي ح يزيد تركيز بعض الأدوية في الدم وهمة حطيت عليهم

1. Erythromycin, telithromycin, and clarithromycin **inhibit cytochrome P450** enzymes and, thus, increase the serum concentrations of numerous drugs, including theophylline, warfarin, cyclosporine, and methylprednisolone.

هايلايتر

همة **narrow therapeutic window** أصلاً

2. They **increase serum concentrations of oral digoxin** by increasing its bioavailability (the antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin, thus leading to greater reabsorption of the drug from the enterohepatic circulation).

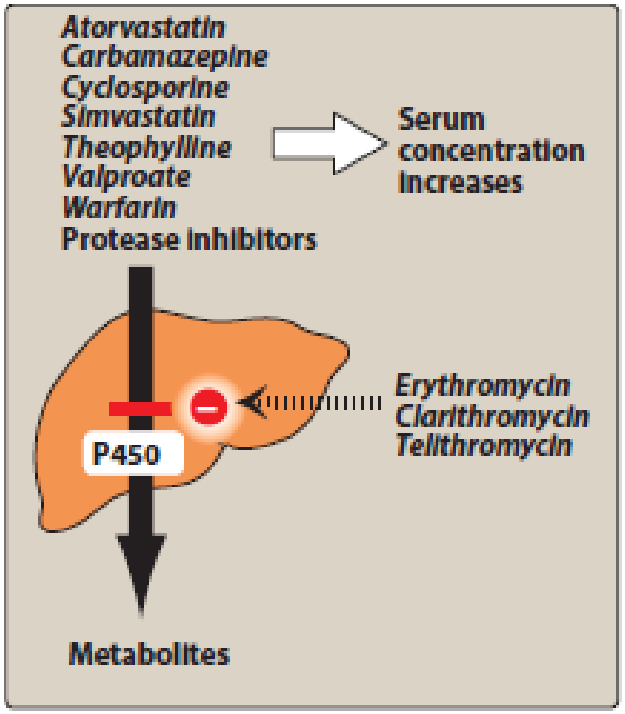
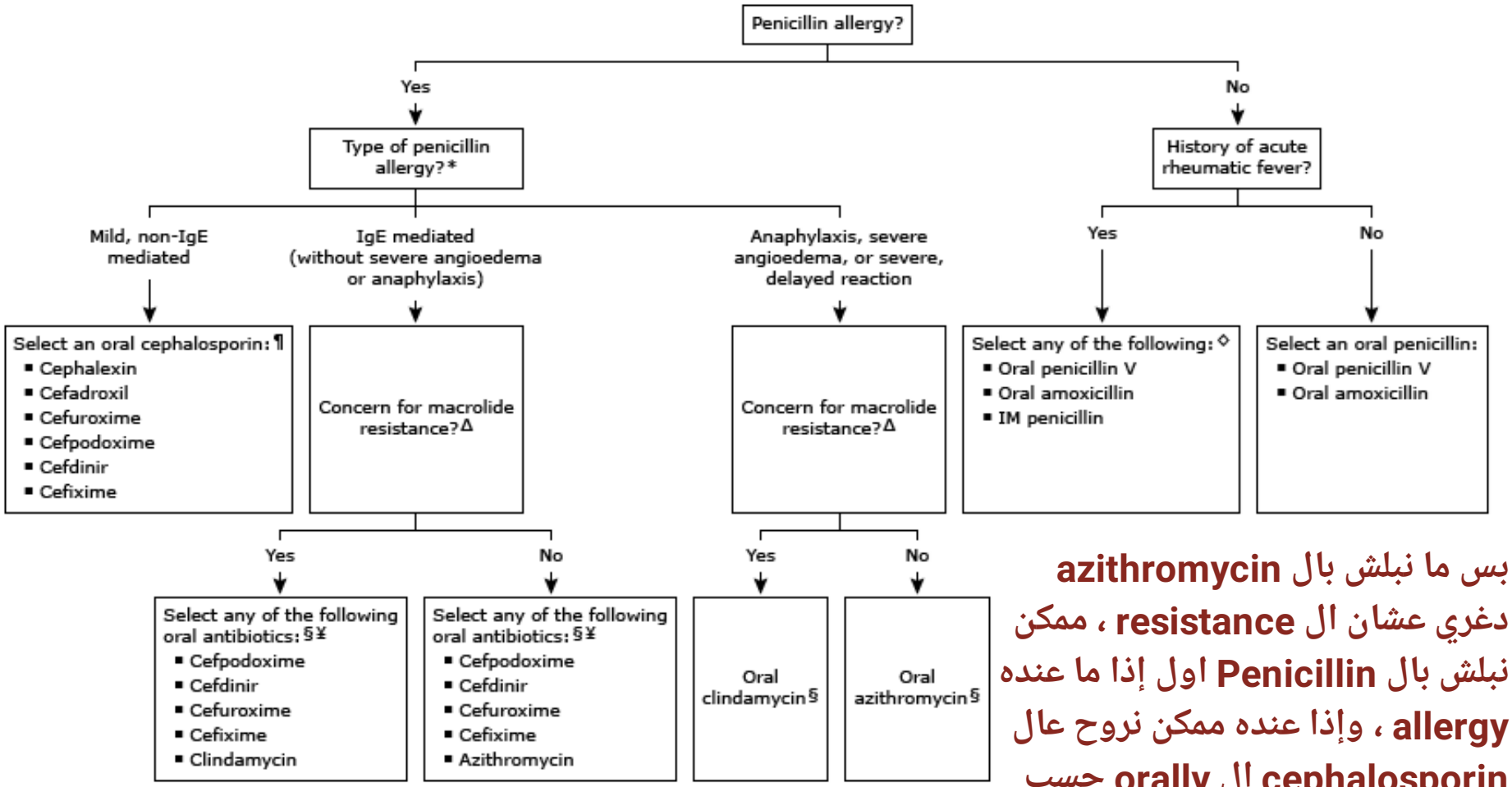


Figure 39.14
Inhibition of the cytochrome P450 system by *erythromycin*, *clarithromycin*, and *telithromycin*.

بوجود ال **antibiotics** هاي ما رح يكون في **intestinal normal flora** وإلّي
هي مسؤولة إنها تعمل ميتابوليزم وتقلل من ال **bioavailability** لل **digoxin**

Treatment of streptococcal pharyngitis

المهم هون نعرف إنه أشهر دواء مستخدم للـ **respiratory** هو الـ **azithromycin**

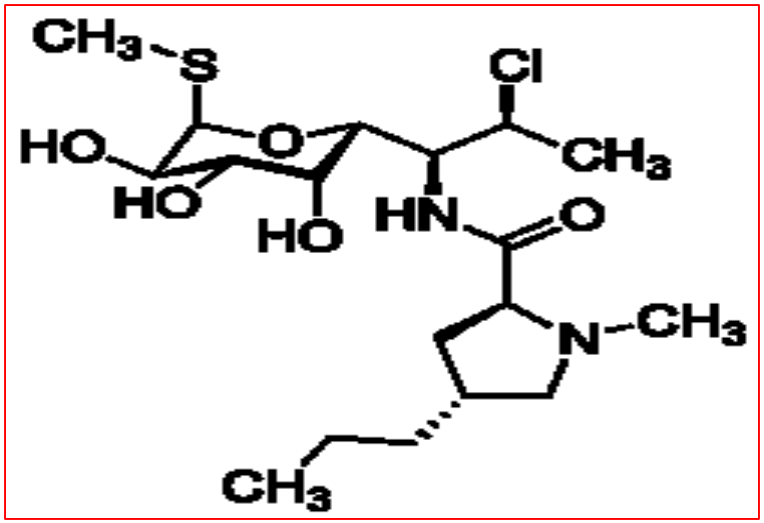


بس ما نبلش بال **azithromycin** دغري عشان ال **resistance** ، ممكن نبلش بال **Penicillin** اول إذا ما عنده **allergy** ، وإذا عنده ممكن نروح عال **cephalosporin** ال **orally** حسب

ما بنعتبره **macrolides** لإنه بختلف بالستركشر

Clindamycin

uses and concerns



Clindamycin

طريقة عمله نفس ال **erythromycin**

- MOA is similar to that of erythromycin (bind to a site on the 50S subunit of the bacterial ribosome. Inhibits protein synthesis)
- Spectrum of activity:

بنستخدمه **orally** لعلاج :

  - Clindamycin is used primarily in the treatment of infections caused by **gram-positive** organisms, including MRSA, streptococcus, and anaerobic bacteria.
  - Topical clindamycin is used for:

أما **topically** :

    - Treatment of acne vulgaris (topical gel, topical lotion, topical solution)
    - Treatment of bacterial vaginosis (vaginal cream, vaginal suppository)

macrolides إلّي حكينا عنهم بال **resistance** نفس ال

- Resistance mechanisms are the same as those for erythromycin, and cross-resistance has been described.
- Side effects: skin rashes, **pseudomembranous colitis** caused by overgrowth of C. difficile **[US Boxed Warning].**
  - Oral administration of either metronidazole or vancomycin is usually effective in the treatment of C. difficile.

metronidazole, vancomycin بنعالجها بال

severe لكن بنفضل بهاي الحالة المريض يوقف العلاج لإنه بتكون الحالة هاي

Antimicrobial regimens for odontogenic soft tissue infections in adults*¶

Clinical entity	Common causative organisms	Antimicrobial regimens
Odontogenic deep space infections		
Normal hosts	*Viridans* and other streptococci, *Peptostreptococcus* spp, *Bacteroides* spp, and other oral anaerobes	Ampicillin-sulbactam 3 g IV every six hours **OR**
		Penicillin G 2 to 4 MU IV every four to six hours **PLUS** Metronidazole 500 mg IV or PO every eight hours **OR**
		Cefoxitin 1 to 2 g IV every four hours **OR**
		Cefotetan 2 g IV every 12 hours **OR**
		Clindamycin 600 mg IV every eight hours[Δ]
Immunocompromised hosts	*Viridans* and other streptococci, *Peptostreptococcus* spp, *Bacteroides* spp, and other oral anaerobes, facultative gram-negative bacilli (including *Pseudomonas aeruginosa*)	Piperacillin-tazobactam 4.5 g IV every six hours **OR**
		Imipenem-cilastatin 500 mg IV every six hours **OR**
		Meropenem 1 g IV every eight hours **OR**
		Cefepime 1 to 2 g IV every 12 hours **PLUS** either:
		Clindamycin 600 mg IV every eight hours **OR** Metronidazole 500 mg IV every eight hours **OR**
		Metronidazole 500 mg IV every eight hours **PLUS** Ciprofloxacin 400 mg IV every 12 hours¶

IV: intravenous; MU: million units; PO: by mouth.
* The doses recommended in this table are intended for patients with normal renal and hepatic function.
¶ Local and institutional rates of antibiotic resistance should be considered before choosing an antibiotic regimen. This is particularly important for immunocompromised patients, since there are substantial rates of fluoroquinolone resistance among *Pseudomonas aeruginosa* and other gram-negative bacteria in some regions.
Δ We reserve clindamycin for penicillin-allergic patients. Resistance to clindamycin among *Prevotella* and *Porphyromonas* spp is increasingly reported.

UpToDate®

الجداول لتثبيت المعلومة 🙄

Antimicrobial regimens for the prevention of dental caries and the treatment of periodontal disease in adults

Clinical entity	Common causative organisms	Antimicrobial regimens
Supragingival dental plaque and dental caries prevention	*Streptococcus mutans*, other streptococci, *Actinomyces* spp	Fluoride-containing toothpaste (sodium fluoride, 1.1 percent or stannous fluoride, 0.4 percent) two or three times daily **AND/OR**
		Fluoride-containing varnishes (sodium fluoride, 5 percent) applied three or four times yearly **AND/OR**
		Chlorhexidine, 0.12 percent oral rinse
Gingivitis		
Acute simple gingivitis	Streptococci, *Actinomyces* spp, spirochetes	Penicillin G 2 to 4 MU IV every four to six hours (OR penicillin V 500 mg every six to eight hours), **PLUS** metronidazole 500 mg PO every eight hours **OR**
		Amoxicillin-clavulanate 875 mg PO every 12 hours or 500 mg PO every eight hours **OR**
		Ampicillin-sulbactam 1.5 to 3 g IV every six hours **OR**
		Clindamycin 450 mg PO or 600 mg IV every six to eight hours
Ulcerative or acute necrotizing ulcerative gingivitis	*Prevotella intermedia*, *Fusobacterium* spp, *Tannerella forsythia*, *Treponema denticoli*, other oral spirochetes	Metronidazole 500 mg PO or IV every eight hours **OR**
		Amoxicillin-clavulanate 875 mg PO every 12 hours or 500 mg PO every eight hours **OR**
		Ampicillin-sulbactam 1.5 to 3 g IV every six hours **OR**
		Clindamycin 450 mg PO or 600 mg IV every six to eight hours
Periodontitis		
Early onset, "aggressive" or "localized juvenile" periodontitis	*Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Treponema denticola*, *Prevotella intermedia*	Doxycycline 200 mg PO or IV every 12 hours (only in patients eight years of age or older) **OR**
		Metronidazole 500 mg PO or IV every eight hours
Adult periodontitis	*Treponema denticoli*, other oral spirochetes, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*	Topical minocycline microspheres (Aristin®) **OR**
		Topical doxycycline hyclate periodontal extended-release liquid (Atridox®)

IV: intravenous; MU: million units; PO: by mouth.

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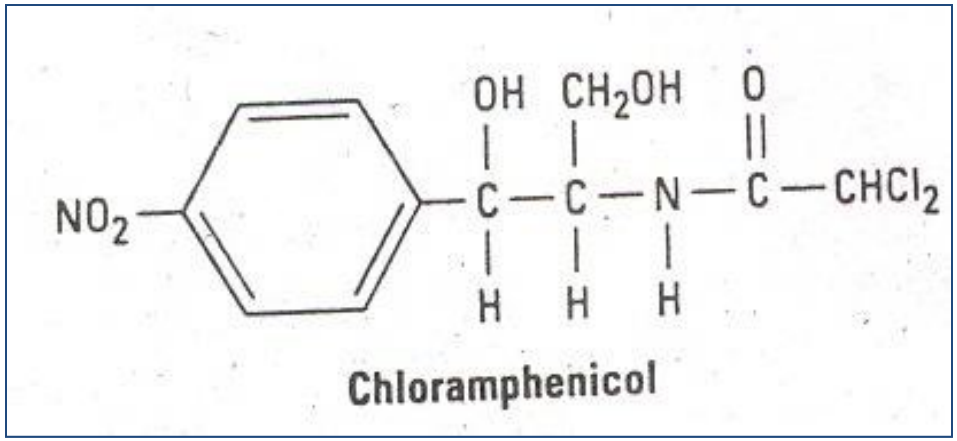
CHLORAMPHENICOL



Chloramphenicol

Chloramphenicol

- Active against a wide range of G+ & G – (including most anaerobic organisms) and Ricketssia
- Because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist with the notable exception of topical treatment of bacterial conjunctivitis (because of its broad spectrum and its penetration of ocular tissues and the aqueous humor.
- It is not effective for chlamydial infections.

بسبب سمّيته ما بنخليه خيارنا الأول بالعلاج لكن أكتر
شي مشهور لاستخدامه هو **bacterial conjunctivitis**
لإنه **broad spectrum+** بصيرله **penetration** عالي

- **MOA**: binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (elongation step, bacteriostatic)

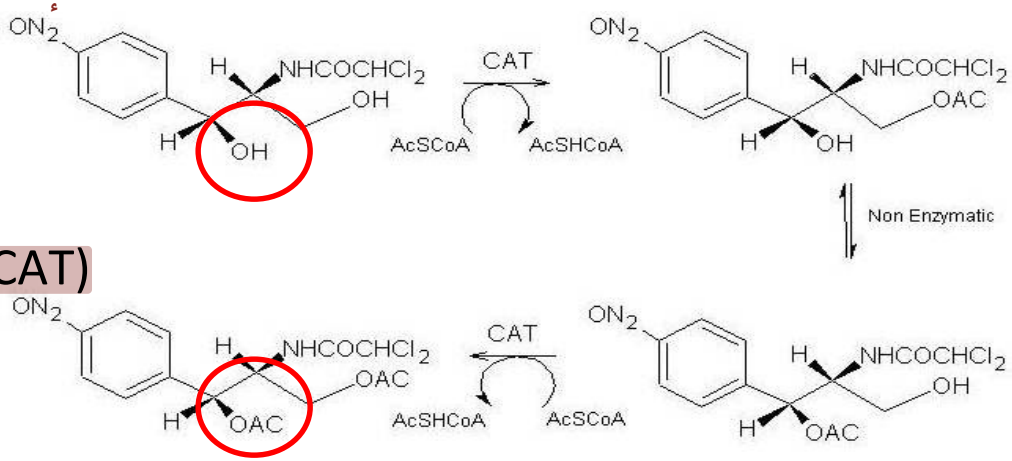
إله ميّزتين : الأولى إنه الوحيد تقريبًا لهسا حكينا إنه ما بيشتغل عال **Chlamydial**
infection + إنه بشتغل عال **elongation step** مش ال **initiation as**
translocation as macrolides and ketolides ولا ال **tetracycline**

Chloramphenicol

إما ما بتخليه يدخل أو بتعمل انزيم يثبط شغله

Resistance:

- Decreased permeability
- Inactivation by plasmid encoded chloramphenicol acetyltransferase (CAT)



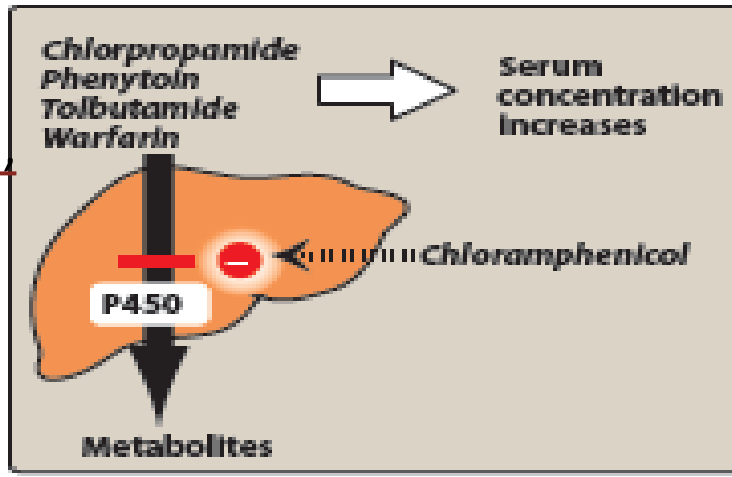
بضيف **acetyl group** عليه ف بخليه **inactive**

Pharmacokinetics:

- Administered IV, widely distributed throughout the body including CSF
- **Metabolized to glucuronide derivative in liver and secreted in urine**

Interactions:

- Chloramphenicol inhibits cytochrome P450
- Blocks the metabolism of warfarin, phenytoin, tolbutamide, and chlorpropamide.



ما في إشي جديد 🤦‍♀️

Adverse effects of Chloramphenicol

السبب إنه بيعمل **inhibition** لل **ribosomes** الموجود بالميتوكندريا

✓ Bone marrow suppression and idiosyncratic aplastic anemias **[US Boxed Warning]**

Due to some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating chloramphenicol levels producing bone marrow toxicity.

لما نعطي جرعة مش محسوبة منه صح لل **Newborn**

✓ Gray baby syndrome (Occurs in neonates if the dose of chloramphenicol is not properly adjusted)

Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol. Consequently, when infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the gray baby syndrome, with vomiting, flaccidity, hypothermia, gray color, shock, and vascular collapse.

تركيز عالي من ال chloramphenicol ⬅️ رح يعمل inhibition of ribosomes الموجود بالميتوكندريا ⬅️ف بالتالي رح يعمل inhibition of protein and ATP synthesis ⬅️ وبنتج عنه bone marrow toxicity

Questions?